REMARKS

1. Status of the Claims

Claims 1-283 are pending in this application. Applicants have renumbered claims 288-293 as claims 278-283 to correct a numbering error. Claims 1-19, 28-69, 73-82, 86-137, 139-163, 165-175, 177-187, and 277-283 are to be considered first for prosecution on the merits. These claims stand rejected under 35 U.S.C. §§112 and 103 (a). The 35 U.S.C. §103 (a) rejections are summarized in a table in the attached Appendix.

2. Rejections Under 35 U.S.C. §112

The Examiner has rejected claims 1-19, 28-40, 43-52 and 277 under 35 U.S.C. §112, second paragraph (OA ¶ 5). Applicants have amended claim 1 in accordance with the examiner's helpful suggestion to recite that a blood sample is withdrawn from the subject prior to conception and in serum or intracellular Th1 immune response and an in serum or intracellular Th2 immune response are measured and these steps are repeated after administering a Th1 antagonist or Th2 agonist to the subject. Applicants submit these amendments fully address this rejection and respectfully request a withdrawal of this rejection.

3. Rejections Under 35 U.S.C. §103 (a)

The Examiner has rejected the claims identified in the attached Appendix in paragraphs 15, and 21-29 of the November 29, 2005 Office Action. The rejections in paragraphs 15 and 23-29 require the combination of Pluenneke with other references identified in the Office Action. The rejections recited in paragraphs 21 and 22 do not require Pluenneke. Rather these rejections require a combination of Coulam with Chaouat et al. (J. Immunol., 1995) (¶21) and Coulam with Chaouat (Cell Immunol., 1994) (¶22).

In Applicants prior response dated August 31, 2005, it submitted a Declaration of Dr. Kwak-Kim under 37 C.F.R. §131 to swear behind Pluenneke. For the reasons set forth in the August 28 Reply, Pluenneke is prior art under 35 U.S.C. §102 (e) and is not a statutory bar.

The examiner has objected to this Declaration stating that the Declaration does not provide sufficient supporting evidence of conception and diligence, it does not state the work was carried out in the United States or other NAFTA country, and lacks the signatures of other joint inventors. Accordingly, Applicants submit herewith a Declaration under 37 C.F.R. 1.131 by joint inventors Dr. Kwak-Kim and Dr. Gilman-Sachs averring that they conceived of the claimed invention prior to April 19, 1999, and worked on this matter diligently thereafter. Exhibit 1 to the Declaration is a letter dated prior to the Critical Date (date has been expurgated) from Dr. Kwak-Kim to a Medical Scientist Liaison of a well known pharmaceutical company stating: "I was glad to hear that your company had an interest in possible anti-TNF application for women with recurrent spontaneous abortions and infertility of immune etiology...I am preparing my idea for a possible clinical study using entanercept."

Further to Dr. Kwak-Kim's study referred to in her letter attached in Exhibit 1 to the Declaration, the joint inventors began development of an assay to measure the ratio of Th1 to Th2 immune responses in a subject. Support of this development effort is shown in laboratory notebook pages (see Exhibit 2 to the Declaration) showing the joint inventors efforts to develop this assay (Declaration ¶7).

The joint inventors further state that they worked on this study diligently from the time of conception to the date when they filed this patent application (¶10). The joint inventors state that they performed all work related to the claimed invention in the United States (¶11). Further, this newly submitted declaration includes the signatures of two of the three joint inventors and the third joint inventor Dr. Alan Beer is deceased. (¶5).

Accordingly, Applicants submit this newly submitted Declaration addresses all of the examiner's objections to the sufficiency of Dr. Kwak-Kim's first declaration, and, therefore, Applicants request that Pluenneke should be excluded as a reference by virtue of this Declaration. Further, the Examiner cannot rely on Pluenneke in any combination, and, therefore, Applicants respectfully request a withdrawal of all the rejections under 35 U.S.C. §103 (a) in paragraphs 15 and 23-29 of the present Office Action as they all require Pluenneke.

As for the rejections that do not require Pluenneke, Applicants have amended independent claims 53 and 73 to include the steps of withdrawing a blood sample from a subject

prior to conception and measuring an in serum or intracellular Th1 immune response and an in serum or intracellular Th2 immune response and administering a therapeutically effective dosage level of a TNF-α antagonist to the subject prior to conception by the subject and withdrawing a blood sample from the subject after administering the TNF-α antagonist and measuring an in serum or intracellular Th1 immune response and an in serum or intracellular Th2 immune response. These steps are not disclosed or suggested by any of the cited references applied in paragraphs 21 and 22 the present Office Action, and, therefore, Applicants submit the rejected claims are patentable over these combination of references and respectfully request a withdrawal of the rejection of these claims under 35 U.S.C. §103 (a).

4. Conclusions

In view of the foregoing, Applicants submit the claims are in condition for allowance and respectfully request an early notice of the same.

Respectfully submitted,

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